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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/533,547 | 03/23/2000 | Randall S. Kent | JAO 28796.02 | 3851 |

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| EXAMINER | |
|---|---|
| MCKANE, ELIZABETH L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1744 | |

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/533,547 | KENT ET AL. | |
| | Examiner | Art Unit | |
| | Leigh McKane | 1744 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 March 2005* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *197-243* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *197-243* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 197-201, 203-205, 234, 235, and 238-243 are rejected under 35 U.S.C. 102(b) as being anticipated by Peterson (U.S. Patent No. 5,730,933).

Peterson teaches the use gamma radiation to sterilize both hard (morselized cancellous bone, other bone sources) and soft (bone marrow) biological materials that are sensitive to radiation, wherein a stabilizer (antioxidant/free-radical scavenger, such as ascorbate or butylated hydroxytoluene) in combination with an extraneous protein (also a stabilizer) is added to the material prior to irradiation and the material is then irradiated within a package "under standard sterilization conditions...at an intensity and for a time duration sufficient to destroy substantially all of the microorganism contamination" (col.4, lines 59-64). See also col.3, lines 35-65; col.4, lines 36-51; col.6, lines 1-18. The material may also be lyophilized or dried with drying agents and/or frozen and placed under a vacuum or inert gas, such as nitrogen or argon (col.4, lines 51-58; col.5, lines 28-35 and lines 53-67). It is noted that contrary to Applicant's arguments, Peterson specifically discloses that the "biologically active composition can also be an osteognic agent...Examples of osteogenic agents comprise...morselized cancellous bone, aspirated bone marrow...and other bone sources." See col.4, lines 2-8. Thus, the biological composition being sterilized *is not* an *extract* of morselized cancellous bone, bone marrow, and other bone sources.

The biological composition *is* the morselized cancellous bone, bone marrow, and other bone sources.

3. Claims 217 and 219 are rejected under 35 U.S.C. 102(b) as being anticipated by Horowitz et al (U.S. Patent No. 5,712,086).

Horowitz et al teaches the sterilization of biological compositions mixed with a stabilizer (mannitol, ascorbate, glutathione, etc.) using gamma irradiation. The biological composition sterilized may be plasma. See col.6, lines 30-35 and lines 61-62; col.7, lines 3-8; Examples 12, 16, 17, and 20. The biological material may be frozen before treatment. See col.7, lines 47-48.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 197, 200, 202-210, 227, 230, 234, 235, and 238-243 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freistedt et al (Abstract of DD 280466) in view of Peterson.

With respect to claims 197, 200, 203, 206, 207, 210, 227, 230, 234, 235, and 238-243, Freistedt et al teaches a method of sterilizing a soft tissue (dural tissue) wherein the tissue is contacted with a combination of two radioprotectants, selected from polyols, lyophilized, and

radiation sterilized. A disclosed radioprotectant is DMSO. The abstract Freistedt et al is silent with respect using gamma radiation, as the radiation source.

Peterson teaches a similar method wherein a lyophilized biological material is contacted with a radioprotectant and sterilized with a suitable dose of gamma radiation. As Peterson evidences that radioprotected, lyophilized biological materials can be safely sterilized using gamma radiation, it would have been obvious to one of ordinary skill in the art to employ gamma radiation as the radiation source in the method of Freistedt et al.

As to claim 202, it is deemed obvious to employ the method of Freistedt et al to sterilize combinations of soft tissue (dural tissue) with hard tissue (such as bone), as one would have had an expectation of success when applying the method of Freistedt et al to other types/combinations of tissues.

With respect to claims 204, 205, 208, and 209, Freistedt et al does not teach maintaining the tissue in an inert or vacuum atmosphere during irradiation. However, Peterson discloses doing both during irradiation of the tissue. See col.5, lines 28-35. As the introduction of an inert gas or the removal of air from the environment will reduce the presence of oxygen and thus, the production of damaging free radicals during irradiation, it would have been obvious to do the same in the method of Freistedt et al.

6. Claim 223 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Peterson or Horowitz et al.

Peterson teaches applying a dose of "about 1 to about 3 mRad" (10-30 kGy). However, Peterson also discloses that the conditions of sterilization are those which at an intensity and a time sufficient "to destroy substantially all of the microorganism contamination". See col.4,

lines 59-64. Similarly, Horowitz et al discloses using a "typical" dose of 40 kGy (col.6, line 61). Regardless, it would have been obvious to increase the total dose as necessary to achieve adequate sterilization, as dose is a known result effective variable.

7. Claims 224-226 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson or Horowitz et al or Friestedt et al.

With respect to claims 224-226, Peterson discloses using the stabilizer in a concentration of about 0.01 to about 10 weight percent (col.4, line 47). Horowitz et al teaches using the stabilizers in "conventional quenching amounts" (col.7, line 9) and the abstract to Freistedt et al is silent to a stabilizer amount. Regardless, one of ordinary skill in the art would have found it obvious to optimize the concentration of the stabilizer as being a result effective variable. Such is within the skill of one in the art.

8. Claims 220 and 221 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al in view of Peterson.

Horowitz et al does not teach maintaining the tissue in an inert or vacuum atmosphere during irradiation. However, Peterson discloses doing both during irradiation of the tissue. See col.5, lines 28-35. As the introduction of an inert gas or the removal of air from the environment will reduce the presence of oxygen and thus, the production of damaging free radicals during irradiation, it would have been obvious to do the same in the method of Horowitz et al.

9. Claims 206-216, 228, 233, 236, and 237 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Horowitz et al (U.S. Patent No. 5,981,163).

With respect to claims 206-211, 215, 216, 228, Peterson teaches the sterilization of

proteins such as globulins, hormones, growth factors, and blood products (albumin), wherein the protein is first stabilized and then irradiated with gamma radiation. The protein may be produced recombinantly. See col.3, lines 40-59. The material may also be lyophilized or dried with drying agents and/or frozen and placed under a vacuum or inert gas, such as nitrogen or argon (col.4, lines 51-58; col.5, lines 28-35 and lines 53-67). Peterson does not disclose the particular claimed stabilizers. Horowitz et al discloses the use of an irradiation stabilizer, selected from polyhydric alcohols (such as mannitol), rutin, glutathione, and others. See col.7, lines 1-7. As Horowitz et al teaches their use in the sterilization of sensitive biological materials with gamma radiation and discloses that these stabilizers are effective in reacting with free radicals, it would have been obvious to use the stabilizer of Horowitz et al in the method of Peterson, especially as Peterson teaches that other antioxidants are acceptable.

As to claims 212-214, Peterson does not disclose the sterilization of clotting factors or immunoglobulins. Horowitz et al discloses that clotting factors such as Factor XIII and fibrinogen, and immunoglobulins such as immunoglobulins G, M, A, and E can all be sterilized using a combination of radiation ($\gamma$) and a stabilizer. See col. 5, lines 60-68. Thus, it would have been obvious to use the method of Peterson to also sterilize clotting factors and immunoglobulins as one would have had an expectation of success in doing so.

With respect to claim 233, Peterson fails to disclose adding a sensitizer to the biological material before irradiation. Horowitz et al teaches sterilizing biological material wherein a sensitizer may be added before irradiation. See col.6, line 64 to col.7, line 10. Horowitz et al disclose that the use of a sensitizer achieves preferential damage to the virus, but not to the

biological material. For this reason, it would have been obvious to add a sensitizer in the method of Peterson.

As to claims 236 and 237, Peterson teaches lyophilization of the product, but does not teach that the solvent removed is an organic solvent. Horowitz et al, however, teaches that it is known in the art to combine a radiation sterilization step with another sterilization step such as treatment with an organic solvent. See col.7, line 66 to col.8, line 7. Since it would have been obvious to first treat the product with a solvent to inactivate viruses, it would have been further obvious to remove the solvent before irradiation.

10. Claim 218 is rejected under 35 U.S.C. 103(a) as being unpatentable over Horowitz et al in view of Zabal et al (abstract of "Contamination of fetal bovine serum with bovine viral diarrhea virus").

Horowitz et al teaches the sterilization of blood products such as plasma but does not teach the sterilization of FBS. Zabal et al discloses that it was known in the art at the time of the invention to employ gamma radiation for the sterilization of FBS. As the method of Horowitz et al is effective in sterilizing blood products while maintaining the biological activity thereof, it would have been obvious to use the method of Zabal et al for the sterilization of FBS.

11. Claim 222 is rejected under 35 U.S.C. 103(a) as being unpatentable over either Peterson or Freistedt et al in view of Peterson, as applied to claims 197 and 206 above, and further in view of Chanderkar et al ("The Involvement of Aromatic Amino Acids in Biological Activity of Bovine Fibrinogen as Assessed by Gamma-Irradiation").

Neither Freistedt et al nor Peterson disclose a rate at which to apply the gamma radiation.

Chanderkar et al teaches sterilization of fibrinogen in lyophilized form in the presence of an electron scavenger (potassium iodide). The preparation is irradiated by gamma radiation with a dose rate of 12,500 R/min (7.5 kGy/hr). See pages 283-284. As the conditions and biological material are similar to those of Peterson and Freistedt et al, it would have been obvious to use the irradiation rate of Chanderkar et al in the method of Peterson or Freistedt et al with Peterson.

12. Claim 227 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson in view of Freistedt et al (Abstract of DD 280466).

With respect to claim 227, Peterson discloses the use of stabilizers in a method of gamma radiation sterilization but fails to teach DMSO as the stabilizer. Freistedt et al teaches a method of tissue sterilization wherein a stabilizer(s) such as DMSO is added to the tissue prior to irradiation. As Freistedt evidences that DMSO is an effective stabilizer for tissue sterilization, it would have been obvious to use in the method of Peterson.

13. Claim 229 is rejected under 35 U.S.C. 103(a) as being unpatentable over Peterson or Peterson in view of Horowitz et al, as applied to claims 197 and 206 above, and further in view of Okrongly et al (U.S. Patent No. 5,283,034).

Peterson discloses the use of stabilizers in a method of gamma radiation sterilization but fails to teach trehalose as the stabilizer. Peterson with Horowitz et al teaches mannitol as a stabilizer. Freistedt et al discloses the use of polyols but is silent with respect to trehalose, specifically. Okrongly discloses that it was known in the art at the time of the invention to add radioprotectants such as polyols or reduced forms thereof to surfaces undergoing radiation sterilization for the purpose of oxygen scavenging. Particularly disclosed are mannitol and trehalose. It would have been obvious to use trehalose as the stabilizer in the methods of either

Peterson or Freistedt et al with Peterson as neither Peterson nor Freistedt et al are limited to the disclosed stabilizers.

14. Claims 231 and 232 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freistedt et al in view of Peterson, as applied to claims 197 and 206 above, and further in view of Okrongly et al.

Freistedt et al teaches the combined use of DMSO and a polyol as radioprotectants during tissue irradiation sterilization. Okrongly discloses that it was known in the art at the time of the invention to add radioprotectants such as polyols or reduced forms thereof to surfaces undergoing radiation sterilization for the purpose of oxygen scavenging. Particularly disclosed are mannitol and trehalose. It is deemed obvious to substitute other known polyol radioprotectants for those used by Freistedt et al where the results are not unexpected.

15. Claim 233 is rejected under 35 U.S.C. 103(a) as being unpatentable over Freistedt et al in view of Peterson, as applied to claims 197 and 206 above, and further in view of Horowitz et al.

Freistedt et al fails to disclose adding a sensitizer to the biological material before irradiation. Horowitz et al teaches sterilizing biological material wherein a sensitizer may be added before irradiation. See col.6, line 64 to col.7, line 10. Horowitz et al discloses that the use of a sensitizer achieves preferential damage to the virus, but not to the biological material. For this reason, it would have been obvious to add a sensitizer in the method of Freistedt et al.

***Response to Arguments***

16. Applicant's arguments filed 02 March 2005 have been fully considered but they are not persuasive. Specifically with respect to claims 197-201 and 203-205, as set forth *supra* Peterson

specifically discloses that the "biologically active composition can also be an osteognic agent...Examples of osteogenic agents comprise...morselized cancellous bone, aspirated bone marrow...and other bone sources." See col.4, lines 2-8. Thus, the biological composition being sterilized *is not* an *extract* of morselized cancellous bone, bone marrow, and other bone sources. The biological composition *is* the morselized cancellous bone, bone marrow, and other bone sources.

17. Applicant's arguments with respect to all other claims have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leigh McKane whose telephone number is 571-272-1275. The examiner can normally be reached on Monday-Wednesday (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Kim can be reached on 571-272-1142. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leigh McKane

**Leigh McKane**
**Primary Examiner**
**Art Unit 1744**

elm
16 May 2005